Stochastic Discrete Effects in a Simple Gene Circuit with Delayed Negative Feedback

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monoribosomes. These ribosome-protected mRNA fragments are purified and prepared for high throughput sequencing to map the position of cellular ribosomes and quantify levels of translation. By comparing ribosome profiling levels with RNA-seq measurements of mRNA levels we find many new cases of genes whose translation only occurs during the proper phase of the cell cycle. We find that a majority of ORFs have a >2-fold change in translation efficiency during the cell cycle. This suggests that *Caulobacter* uses cell cycle-specific regulation of translation to ensure proper timing of gene expression.

Computational Systems Biology

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Modelling the Mechanics of the Circulation: Blood Rheology and Atherosclerosis

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In this work, we test the hypothesis that a redistribution of blood particles is related to predilection sites of atherosclerosis,which is characterised by the deposition of lipid material and inflammatory cells. The focal distribution of lesions, shear stress,and mass transport play an important role[1] because shear stress scales inversely with enhanced transport of species in the vessel wall. Also, because 46% of blood volume is made up of particles, blood compounds have wide-reaching effects on the coupling of blood flow to the vessel walls. Indeed, some works have shown changes in flow rate, apparent viscosity and flow patterns due to particle's shape and/or concentration[2,3,4,5,6] besides literature usually focus on microcirculation that is driven by diffusive transport and differs in many other ways to the mechanics of circulation in large vessels. Here, we present some results(Fig.1) to support the hypothesis that flow trends related to atheroma development might be more accurately described by multiphase flow models[7], which is the subject of ongoing research.

[1] C.G.Caro, Arterioscler. Thromb. Vasc. Biol. (2009).
[2] M.Zastawny et.al., J. Multiph. Flow (2012).
[3] G.Pereira, Biophysical Journal (2013).
[4] K.Sugiyama et.al., J. Comput. Mech. (2010).
[5] G.Pereira. Multiscale Modelling in Medicine and Biology Conference (2012).
[6] F.Thomas, M.Sc. Thesis, Imperial College London (2012).
[7] B.Wachem's Group, Multiflow: http://www.multiflow.org/

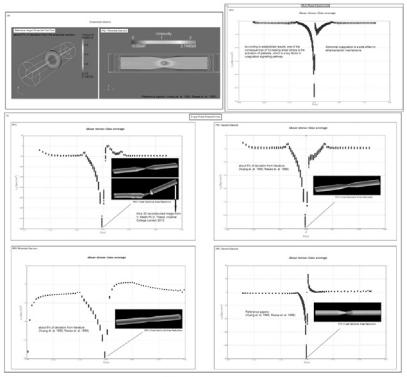

Fig. 1 Blood Flow Phenomena $Re = 100$: (a) Streamwise velocity in a Poiseuille pipe flow compared to a model of moderate lumen narrowing; (b) Poiseuille single phase – patterns of shear stress considering four levels of lumen narrowing in atheroma development; (c) Pulsatile multi phase: the shear stress for a model of severe lumen narrowing increases compared to Poiseuille single phase results.

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Stochastic Discrete Effects in a Simple Gene Circuit with Delayed Negative Feedback

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Negative feedback loops are ubiquitous motifs in gene regulation processes, providing cells with control mechanisms to perform key decisions. Consequently, they have received a lot of recent attention in the efficient design of synthetic gene circuits. The interconnected biochemical reactions composing negative feedback loops are discrete and random by nature, and are more accurately described by stochastic models. These models, however, often make assumptions yielding erroneous predictions, or simply miss out on important discrete stochastic effects. One such common omission is the explicit delays that separate the initiation of transcription and translation from the appearance of their corresponding functional products. Thus, delay-induced stochastic oscillations and other delay-induced stochastic discrete effects have remained relatively unexplored at the single-cell level. In our work (Zavala and Marquez-Lago, submitted), we study oscillatory and multimodal behavior in a simple gene circuit with delayed negative feedback by systematically analyzing the influence of negative feedback strength and transcriptional/translational delays on expression dynamics. We carry out single-cell simulations producing exact trajectories of the Delay Chemical Master Equation, thus avoiding any approximation errors, and demonstrate an oscillatory regime emerges through a stochastic Hopf bifurcation. Furthermore, we characterize conditions under which stochastic oscillations produce bursts, and vice versa. In conformity with previous results (Marquez-Lago et al., BiophysJ 2010) we show that the same gene circuit architecture is capable of multimodal behavior and burst-like expression. Most importantly, we describe how explicit delays produce novel non-classic effects, not yet reported in the literature.

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Predicting and Retrodicting Fate Patterns in C. elegans Vulval Development using Logic Programming

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Vulval development in *C. elegans* is a paradigm for understanding how cell fate determination leads to organogenesis. The fate pattern of a row of six cells is specified by spatial and temporal controls, and the competition of the LET-23/SEM-5/LET-60/MAPK and Delta/Notch signalling pathways. Formal verification techniques applied to state models of vulval development have been shown as a powerful approach for demonstrating how the signalling systems interact and determine cell fate. However, the computational requirements of verification approaches become prohibitive as model complexity increases. Here we apply a logic programming based approached to derive minimal models of vulval development, increasing the speed of prediction of fate pattern from genotype by up to four orders of magnitude. This increase in speed further allows us to infer or 'retrodict' genotypes from the final fate pattern. We apply this new technique to understand how highly variable cell fates arises when the precise morphogen gradient of LIN-3 is effectively randomised by diffusion in *dig-1* mutations. We further apply this to the study of *let-23* mosaic mutations, and find that the resulting model refinements reconcile our approach with historical experimental data. Based our new findings we propose that logic programming provides an efficient approach for design and analysis of experimental data.

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Modeling Electrical Activity in Intestinal L-Cells

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Glucagon-like peptide 1 (GLP1) is an insulinotropic hormone released from intestinal L-cells in response to food ingestion. It is responsible for the so-called incretin effect, i.e. the fact that glucose ingested orally elicits a greater insulin response than glucose administered intravenously, even when glucose concentrations in plasma are matched.

In addition, GLP1 inhibits glucagon secretion, slows gastric emptying, regulates appetite and food intake. All these actions have made GLP1 an appealing target for the development of new treatments of type 2 diabetes. In this context, the comprehension of the sensory and secretory pathways, which is still poorly understood, becomes essential. The stimulus-secretion pathway in L-cells includes electrical activity to transduce glucose sensing to calcium-stimulated exocytosis.

We build a mathematical Hodgkin-Huxley-like model of electrical activity of L-cells based on recent data on primary colonic L-cells. The model includes ATP-sensitive K+-channels (K(ATP)-channels), voltage gated Na^+- and K+-channels and low- and high-voltage activated Ca^{2+}-channels. The model incorporates also the sodium glucose cotransporter SGLT1, which has been reported to be the primary glucose sensing machinery in L-cells.

The model reproduces satisfactorily electrical activity consisting of action potentials in response to glucose. A role for sodium and calcium channels for the upstroke, and activation of potassium channels for the downstroke, is demonstrated by simulating ion channel blockage. Electrical activity is a result of the inward current due to sodium-glucose cotransport, proving the central role of SGLT1. K(ATP)-channel closure is shown to contribute to electrical activity, since lower K(ATP)-conductance reduces the threshold for SGLT1 conductance where electrical activity is initiated.

The model is shown to be useful for hypothesis testing and as a starting-point for future investigations of the signals underlying GLP-1 secretion, which might eventually lead to new antidiabetic drugs aiming at increasing endogenous GLP-1 release.

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Investigation of Novel Zap-70 Functionality in T Cell Signaling Pathways using Computational Modeling

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Aberrant regulation of cellular processes in immune systems can result in human disease. Therefore, we need a better understanding of the mechanistic